REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-6, 8, 10 and 14-18 are pending in the application subsequent to entry of this Amendment.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention, to address claim clarity issues raised on pages 4-5 of the Official Action, to reduce issues and to advance prosecution generally.

Claims directed to compounds *per se* have been revised to refer to a single compound and adjusted to include proper terminology, as appropriate. Claims 7 and 9 have been canceled to reduce issues, claim 10 revised to depend from claim 8. Claims 11-13 have been canceled and replaced with new method claim 15-18. New claim 14 has been added directed to the specific amino acids listed in the first paragraph of page 7 of the description. Further comments regarding the claim amendments will appear in the discussion that follows.

Claims 9-13 – 35 USC § 112

Claims 9 and 11-13 are canceled and replaced with new method of treatment claims 14-18. Claim 10 is dependent from claim 8 directed to a pharmaceutical composition; claim 10 should not have been included in this rejection. This response is made on the basis of new claims 14-18.

Camptothecins are a well-known class of antitumor drugs used for the treatment of different tumors. The description of the invention makes explicit reference to EP 1 044 977 (EP '977) and the literature cited therein. This reference reports that camptothecins demonstrated a wide spectrum of antitumor activity, in particular against colon tumors, other solid tumors and leukemias (see page 1, fourth paragraph). The clinical reference for camptothecins is Topotecan, which is indicated for the treatment of small and non-small cell lung, ovarian, breast, stomach, liver, prostate, soft tissue sarcoma, head and neck tumors, cancer of the esophagus, resistant colon-rectum, multiform glyoblastoma, and chronic and acute myelocytic leukemias (EP'977, page 3, third paragraph). The compounds disclosed in EP'977, of which the compounds of the present invention are derivatives as far as the 7-C(R_5)=N-O-R_4 substituent is concerned, and the activity on a wide range of tumors is proven by the enclosed list of references retrieved from PubMed (Annex 4). See also Penco et al., US 6.242.457, claiming priority of EP'744, where the range of treated tumors was expanded (note column 14).

Further evidence of a wide range of antitumor activity is found in the same references as cited by the examiner, (*see* WO'691).

Therefore, the state of the art as to the therapeutic benefits to be obtained from the camptothecins must be recognized, since there is no reason for one skilled in this art to believe that the claimed compounds would not be effective on different tumors. To the contrary, the problem solved by the present invention is to enhance stability and solubility in water of the molecule, thus enhancing the pharmacological activity and giving a person skilled in the art a more powerful therapeutic tool in terms of an improved therapeutic index; *see* page 2, last line.

The present compounds are not claimed for treating tumors which are not usually treated with Topoisomerase I inhibitors or with camptothecins in general. This is very clear from the entire content of the description and the references cited in it and is clearly stated in new claims 15-17. Therefore, the skilled clinician will know for which type of susceptible tumors the compounds can be used.

The activity of camptothecins in parasitic and viral infections is also well-known in the art (see WO'876, page 23, first full paragraph) and thus is claimed in new claim 18.

In view of the above, applicants respectfully request withdrawal of this rejection.

Claims 1, 4-6, 7 and 9-13 – 35 USC § 112

Claim 1: there are only two cases for n and m:

1) both n and m are 1;

2) both n and m are 0.

No other cases are disclosed and this is clarified in amended claim 1.

The definition of residue B as amino acid is clearly explained on page 7, first paragraph of the description and claim 1 is amended to reflect this description. New dependent claim 14 is added directed to the amino acids specified in this passage.

R_4 seems clearly defined by the list of variables in claim 1. The term "residue" has been replaced with "substituent".

The spelling of "benzylglycil" has been corrected in claim 4.

Claim 5: actually, step b) as written is self-explanatory. Substitution of the leaving group with the Y group is a well-known class of chemical reactions, also known as nucleophilic substitutions. Please see the attached chapter of a university textbook (Annex 1) explaining the

mechanism of nucleophilic substitution reactions. The term "substitution of said leaving group with the Y group" recited in claim 5 is sufficient to indicate to the skilled person what to do to carry out the claimed process to obtain the desired product. In any event, all one has to do is look in applicants' specification. Claim 5 is supported by the description, see page 10, "preparation of the intermediate products 2a,b" and page 11, "preparation of the intermediate products 4a,b". Claim 5 will be interpreted in light of the description.

Claim 6: also step b) is self-explanatory as written. Transformation of a carboxylic group into an amide is a well-known chemical reaction. Please see the attached copy of a chapter of a university textbook (Annex 2) showing different modes for obtaining an amide. In any event, all one has to do is look in applicants' specification. Claim 6 is supported by the description, see page 11, "preparation of the intermediate products 6a,b" and page 12, "preparation of the intermediate products 7a,b" and "preparation of the products 8a,b". Claim 6 will be interpreted in light of the description.

Claim 7 has been deleted.

Claim 9 has been deleted.

Claim 10, a pharmaceutical composition claim dependent from claim 8, is maintained. Applicants believe this claim is clear to the skilled reader, since combining different antitumor drugs is common practice in this field. The other antitumor drug will be determined by the skilled person simply exercising his or her knowledge. Attached are only the only first 50 titles out of 269 reviews published until 2002 (priority year of this application) to show the current knowledge of cancer polychemotherapy (Annex 3).

The subject matter of claims 12 and 13 is maintained and written as methods of treatments in new claims 14-17, since applicants believe that the skilled person will know how to use the invention just resorting to common knowledge. A sample of literature is enclosed (Annex 5). The examiner has already indicated the treatment of lung tumor is enabled; *see* item 4, second line and compare with new claim 17. Claim 16 is directed to a particular group of susceptible tumors described in the paragraph bridging pages 13-14 of the specification.

Claims 1, 3, 5, 7-9 and 12 – 35 USC § 102(b)

Claim 1 has been amended by deleting the meaning of hydrogen for the R_1 group. This amendment restores novelty over Vishnuvajjala.

Claims 1, 2, 4 and 6-13 – 35 USC § 103(a)

The Examiner admitted that the prodrug disclosed by Matsumoto et al. is an HIV protease inhibitor, but is of the opinion that the document affirms the general applicability of the approach and points at Figure 2 to support the opinion.

The Matsumoto et al. reference is cited in the subject application (page 2) with the following comment: "*molecule of a dipeptide nature, differing enormously from the molecular structure of camptothecin, and to that end functionalise a hydroxyl group with a portion formed by a spacer part and a solubilizing part. The spacer part is provided by a bicarboxylic acid, whereas the solubilizing part is provided by a diamine*".

Matsumoto et al. give only more than general comments on the possible solubilizing effect of the system provided by them, namely the spacer and the solubilizing portion, the latter releasing the drug through a cyclization mechanism.

The skilled person must find in the prior art a clear teaching of the case this person is facing, with all instructions and indication on how to obtain the expected results. In the present case, Matsumoto et al. with all its insufficiencies does not apply, neither alone nor in combination with Penco et al.

Penco et al. mention the problem of water-solubility of camptothecin derivatives, but give no indication on how to solve this problem.

Matsumoto et al. enable only for a dipeptide derivative. Therefore, this reference is not predicable for camptothecin derivatives, which are polycyclic compounds of a completely different chemical nature.

Secondly, Matsumoto et al. put very strict rules in designing the prodrug: a) only succinic or glutaric dicarboxylic acids are provided, and a short chain amine as solubilizing portion are disclosed. The final teaching of Matsumoto et al. is to find suitable conditions to enhance cyclization of the spacer-solubilizing system, and this leads to short chain elements ending with an amino group. The authors advise against different ending groups (see page 608, right column).

Ultimately, Matsumoto et al. teach a solubilizing system which will cyclize and release the drug. There is the least suggestion that such a system with strict rules will work with 7-substituted camptothecins derivatives, as the claimed ones.

Moreover, the present invention goes against Matsumoto et al. teaching, by providing a wide range of chain length (from 1 to 8 carbon atoms) and a wide variety of terminal groups other than a simple amino group.

Therefore, Matsumoto et al. give no expectation to successfully solve the problem of water-solubility passing from a dipeptide derivative, such as the only enabled compound KNI-727, to a complex polycyclic compound, bearing a complex substitution in position 7, such as the camptothecin derivatives of the present invention.

For the above reasons it is respectfully submitted that the claims of this application are in proper order, enabled and define subject that is patentable over the cited and applied prior art references. Reconsideration and favorable action are solicited. Should the examiner have any questions or require further information, please contact the undersigned.

Respectfully submitted,

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ANNEX 1

A Series of Books in Organic Chemistry
Andrew Streitwieser, Jr., Editor

INTRODUCTION 1

ORGANIC CHEMISTRY

Andrew Streitwieser, Jr.
Clayton H. Heathcock
University of California, Berkeley

Macmillan Publishing Co., Inc.
NEW YORK

Collier Macmillan Publishers
LONDON

CHAPTER 8
Reactions of Alkyl Halides

8d
The Displacement Reaction

The replacement of the halogen in an alkyl halide by another group is one of the most important reactions in organic chemistry. In Section 3.1, we took a brief look at one such reaction, the reaction of methyl chloride with hydroxide ion.

$$HO^- + CH_3Cl \xrightarrow{H_2O} CH_3OH + Cl^-$$

Another example is the reaction of ethyl bromide with potassium iodide in acetone solution.

$$CH_3CH_2Br + K^+I^- \xrightarrow{\text{acetone}} CH_3CH_2I + KBr\downarrow$$

Although this is an equilibrium process, the reaction proceeds virtually to completion because potassium iodide is soluble in acetone and potassium bromide is not.

Like the reaction discussed in Section 3.1, the reaction of ethyl bromide with iodide ion is relatively slow. In order for complete reaction to occur, it is necessary to heat the mixture for several hours. The rate of the reaction may be determined by following the rate of disappearance of reactants or the rate of appearance of products. It is proportional to the *product* of the concentrations of the two reactants.

$$\text{rate} = -\frac{d[C_2H_5Br]}{dt} = -\frac{d[I^-]}{dt} = \frac{d[C_2H_5I]}{dt} = \frac{d[KBr]}{dt} = k[C_2H_5Br][I^-]$$

This equation is expressed in the symbolism of calculus. The expression

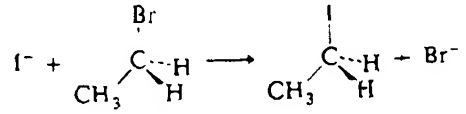
$$\frac{d[C_2H_5Br]}{dt}$$

means simply the rate with which the concentration of C_2H_5Br changes with time. The negative sign indicates that the concentration of C_2H_5Br decreases as time increases. Note that in this case [KBr] refers to amount rather than concentration because of its low solubility in acetone.

The concentrations of C_2H_5Br, I^-, C_2H_5I, and KBr may be determined at different times during the reaction by chemical or spectroscopic analysis. As the reaction proceeds, the concentrations of the reactants become reduced and the rate of reaction decreases. For example, at 50°, with the two reactants each present in an initial concentration of 0.1 *M*, the reaction is 50% complete in 7 min but only 95% complete after 2 hr. Furthermore, the reaction has an activation energy, $\Delta H^{\ddagger}$, of 19 kcal mole^{-1}; it is 10 times slower at 25° than it is at 50°. This activation energy is considerably higher than those of the free radical reactions we studied in Chapter 5.

When the rate of a chemical reaction depends on the concentration of two

species, as in this case, it is said to display **second order kinetics**. This suggests a **bimolecular** mechanism, one in which one molecule of each reactant collide and react. The relatively high activation energy shows that only a minute fraction of such collisions actually result in reaction—those involving reactant molecules with sufficient kinetic energy. We might imagine that a straightforward mechanism would be one in which the attacking group, I^- in this case, simply displaces the *leaving group*, Br^-, from its bond to carbon.



However, a large mass of evidence has been accumulated which shows that this **front-side** attack is *not* the mechanism of this reaction.

> This does not mean that this is not a perfectly good mechanism, only that another mechanism is better for this particular reaction. The activation energy of the frontal-attack mechanism is so much higher than that of the actual mechanism that no significant number of product molecules are formed by such a path. Since rates are exponential functions of activation energy, a small energy change can have a dramatic effect on rate. For example, if two reactions differ in activation energy by 10 kcal $mole^{-1}$, the ratio of their reaction rates is 10,000,000 : 1. Thus, it is only necessary that we consider the most probable reaction mechanisms for a given reaction—those with the lowest activation energies.

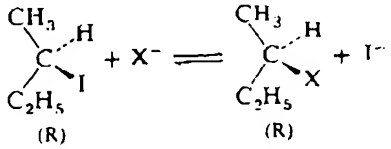
Instead of such a simple frontal attack, the reaction actually proceeds by a more complex mechanism that involves attack at the *rear of the C—Br bond.*

8.2 Stereochemistry of the Displacement Reaction

It has long been known that, when an optically active alkyl halide is exposed to halide ion in solution, the optical activity gradually diminishes to zero. This is an example of racemization; the optically active halide is converted to an equimolar mixture of (+) and (−) enantiomers. The rate of racemization is dependent on the concentration of both the alkyl halide and the added halide. The rate constant for the racemization process is called k_a. The conditions under which such racemization occurs are the same as those that lead to substitutions such as those discussed in Section 8.1.

The fact that optical activity is lost shows unequivocally that the frontal-attack mechanism cannot be the sole mechanism for such substitution reactions, because that mechanism leads to retention of absolute configuration at the asymmetric atom. For example, if the frontal-attack mechanism were the only mechanism for substitution in (R)-2-iodobutane, then a system containing this optically active halide would always contain only alkyl halides of the (R) configuration.

frontal attack mechanism:



(R) (R)

There must be a mechanism for substitution that allows racemization at C-2. To

determine how often each replacement of one halide by another is accompanied by a change from the (+) enantiomer to the (−) enantiomer, it is necessary to know both the rate of racemization and the rate of the substitution reaction itself.

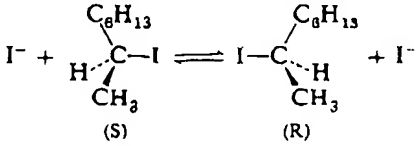
This experiment was first done in 1935 by the late Professor E. D. Hughes and his colleagues at the University of London. The experiment was an extremely elegant one, which used sodium iodide containing a radioactive isotope of iodine, ^{128}I, as the attacking group and optically active 2-iodooctane containing normal ^{127}I as the alkyl halide.

^{128}I is prepared by exposing normal ^{127}I to neutrons. The radioisotope decays with a half-life of 25 min.

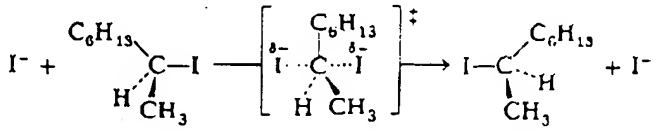
At equilibrium, the radioactive iodine is distributed equally between 2-iodooctane and iodide ion.

$$^{128}I^- + C_6H_{13}\overset{\displaystyle I}{\underset{|}{C}}HCH_3 \rightleftharpoons I^- + C_6H_{13}\overset{\displaystyle {}^{128}I}{\underset{|}{C}}HCH_3$$

The reaction was found to have a rate constant at 30°, $k_{exch} = (1.36 \pm 0.11) \times 10^{-3}\ M^{-1}\ sec^{-1}$. Under identical conditions, the rate constant for racemization of optically active 2-iodooctane was found to be $k_a = (2.62 \pm 0.03) \times 10^{-3}\ M^{-1}\ sec^{-1}$. Within experimental error, *the rate of racemization is exactly twice that of exchange*. Consequently, each act of replacement of one iodide by the other is accompanied by a change from one enantiomer to another. In this way, the rotation of one molecule of product cancels that of one reactant molecule, and is equivalent to two molecules of racemic material. Looking at it in a slightly different way, *all* of the beginning molecules must undergo reaction with $^{128}I^-$ before incorporation of the radioisotope is complete, whereas only one half of the beginning molecules must undergo inversion of stereochemistry before racemization is complete. Thus, if inversion of stereochemistry occurs every time substitution occurs, k_a must be exactly twice k_{exch}, as is found.



This observation has been combined with many other studies to infer that, in a bimolecular displacement reaction, the attacking group attacks at the carbon atom at the rear of the bond to the leaving group. During reaction, the carbon forms a progressively stronger bond to the attacking group, while the bond to the leaving group is being weakened. During this change, the other three bonds to the central carbon progressively flatten out and end up on the other side of the carbon in a manner similar to the spokes of an umbrella inverting in a windstorm.



The reaction is formulated as above, with the transition state geometry in brackets. The dotted lines indicate a partially formed or partially broken bond. The symbol

δ^- indicates that the negative charge is spread over both iodines in the tra state.

During the course of the reaction, the reacting system has greater pe energy than either the reactants or the products. The two weak bonds entering and leaving groups are weaker than the single bond in either the r or the product. Hence, energy is required in order for reaction to occ necessary potential energy is supplied by the conversion of kinetic ener only the minute fraction of reactants that have sufficient kinetic energy ca Furthermore, even if the colliding reactants have sufficient kinetic energ must have the proper orientation or they will simply bounce apart. Rec the point of highest energy is called **the transition state.** It is important to r ber that the transition state is a point of *maximum* energy. It is not a molecule that can be isolated and studied. In fact the whole act of displa occurs in the space of about 10^{-12} sec, the period of a single vibration. system has the transition state geometry for only a fleeting moment.

The geometry of the transition state appears to be that in which the in and leaving groups are both weakly bonded to carbon in a linear fashi in which the three remaining bonds to carbon lie in a plane perpendic the two weak bonds. The reaction mechanism for reaction of an entering Y^-, and a leaving group, X^-, is shown in Figure 8.1, where the structure reacting system at several points along the reaction coordinate is illustra point (b) the C—X bond has started to lengthen and the central carbon has to flatten out. At the transition state, point (c), the central carbon is approx flat and both the bonds to the leaving and entering group are long. Pe

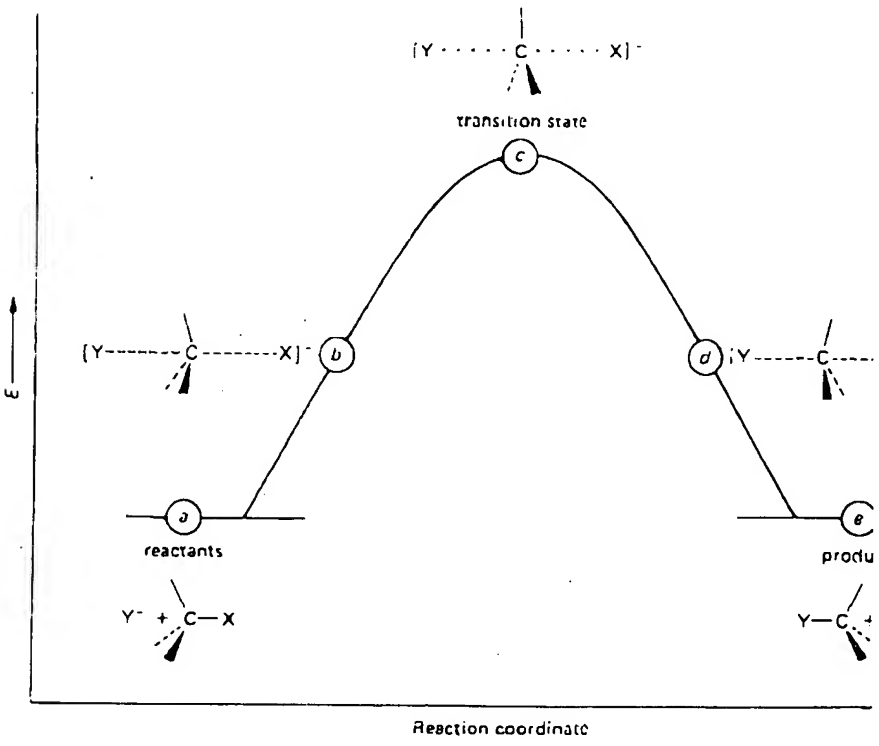


FIGURE 8.1 *Reaction mechanism profile for a displacement reaction by* Y^- RX

occurs on the final road to products (e); the central carbon has bent, the C—Y bond is approaching normal length, and the leaving group, X, is receding. The structures at points (a) through (e) are represented in stereo form in Figure 8.2.

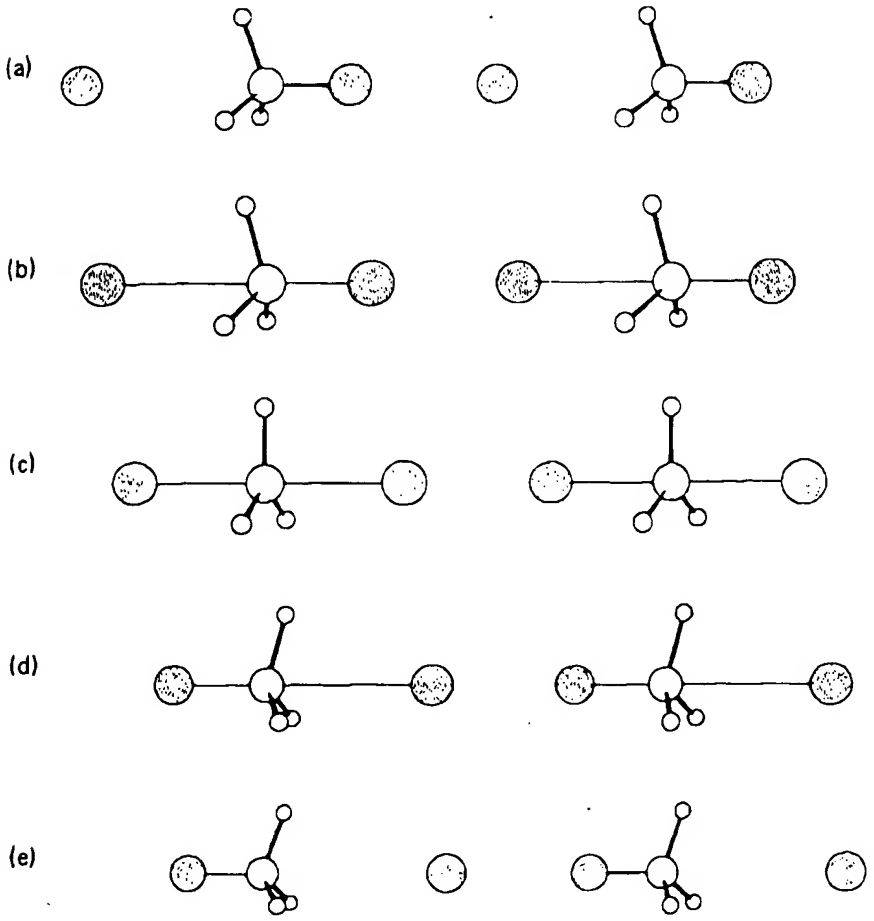


FIGURE 8.2 *The structure of the reaction system at points* (a) *through* (e) *in Figure* 8.1.

In orbital terms, both the reactant and the product are tetrahedral. The C—X bond in each case is C_{sp^3}-X. In the transition state, the weak bonds to X and Y may be considered to derive from overlap of a halogen orbital with the two lobes of a *p* orbital on the central carbon. The other three bonds to this carbon are formed from sp^2 hybrid orbitals, as shown in Figure 8.3

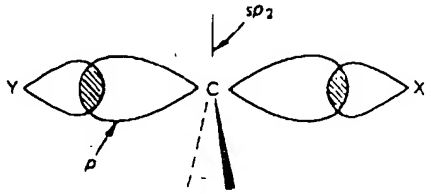


FIGURE 8.3 *Orbital formulation of the transition state of a displacement reaction.*

8.3 Generality of the Displacement Reaction

The importance of the displacement reaction lies in its generality. Althc the reaction was introduced in the preceding sections with halide ions as ente groups, analogous reactions are known with a wide range of anions and ne molecules. The only requirement is that the attacking group be a Lewis l a species which contains an atom that has a pair of electrons available for bon The examples in Table 8.1 demonstrate the range of attacking groups that und the reaction.

A base may generally be regarded as the conjugate base of an acid, a may be neutral or charged.

$$BH \rightleftharpoons B:^- + H^+$$

$$BH^+ \rightleftharpoons B: + H^+$$

conjugate acid — conjugate base

A quantitative measure of the **basicity** of a base is the acidity, or pK_a,* conjugate acid.

$$K_a = \frac{[B^-][H^+]}{[BH]} \quad \text{or} \quad \frac{[B:][H^+]}{[BH^+]}$$

$$pK_a = -\log K_a$$

A weak conjugate acid (more positive pK_a) corresponds to a strong base; a s

TABLE 8.1
Some Displacement Reactions with Ethyl Bromide

Attacking Reagent:		Product	
Formula	Name	Formula	Name
HO^-	hydroxide ion	C_2H_5OH	ethyl alcohol
$C_2H_5O^-$	ethoxide ion	$CH_3CH_2OCH_2CH_3$	diethyl ether
HS^-	hydrosulfide ion	CH_3CH_2SH	ethanethiol
SCN^-	thiocyanate ion	CH_3CH_2SCN	ethyl thiocyanate
CN^-	cyanide ion	CH_3CH_2CN	ethyl cyanide, propionitrile
N_3^-	azide ion	$CH_3CH_2N_3$	ethyl azide
NH_3	ammonia	$CH_3CH_2NH_3^+ Br^-$	ethylammonium bromide
H_2O	water	$CH_3CH_2OH_2^+ Br^-$	ethyloxonium bromide
$CH_3CO_2^-$	acetate ion	$CH_3CO_2C_2H_5$	ethyl acetate
NO_3^-	nitrate ion	$CH_3CH_2ONO_2$	ethyl nitrate
$P(CH_3)_3$	trimethylphosphine	$C_2H_5P(CH_3)_3^+ Br^-$	ethyltrimethyl-phosphonium bi
$N(C_2H_5)_3$	triethylamine	$(C_2H_5)_4N^+Br^-$	tetraethylammoniu bromide

*For a review of pK_a see sections 11.4, 17.4, and Appendix IV.

conjugate acid (less positive pK_a) corresponds to a weak base. A few common bases, with the pK_as of the corresponding conjugate acids, are given in Table 8.2. Other values are given in Appendix IV.

The basicity of a base depends on the strength of its bond to a proton in solution. In the displacement reaction, the base forms a bond to carbon. Consequently, we might expect to find some correlation between the energy involved in the protonation of a base and the activation energy for its reaction in a displacement reaction. Instead of energies or enthalpies, many correlations of this type have been found using the Gibb's free energies, ΔG. The pK of an acid is proportional to the standard free energy of the acid-base equilibrium:

$$\Delta G^\circ = 2.303\, RT\, pK$$

This equation follows by combining the relation between an equilibrium constant and the standard free energy with the definition of pK.

$$\Delta G^\circ = -RT \ln K$$

Recall from Chapter 3 that rate constants are also related to free energies of activation, $\Delta G^\ddagger$

$$k = \text{constant} \times e^{-\Delta G^\ddagger/RT}$$

$$-\log k = \frac{\Delta G^\ddagger}{2.303\, RT} - \log(\text{constant})$$

To test the existence of a correlation between basicity and reactivity in displacement reactions, we first need to determine the second-order rate constants for reaction of a series of bases with some common substrate under the same experimental conditions; that is, for the same solvent and temperature. Next, we plot the logarithms of these rate constants against the corresponding pK_a values. For a perfect correlation every point will fall exactly on a straight line. Figure 8.4 shows a plot of this type for the reactions of a series of bases with methyl iodide in methyl alcohol solution. We see that there is a rough correlation in the anticipated direction. There is a tendency for bases with high pK_a (stronger bases) to react faster with methyl iodide. The points cluster in a linear fashion but there is a good deal of scatter.

TABLE 8.2
Some Common Bases

Base	Conjugate Acid	pK_a
I^-	HI	−9.5
Br^-	HBr	−9
Cl^-	HCl	−7
HSO_4^-	H_2SO_4	−5
H_2O	H_3O^+	−1.7
F^-	HF	3.2
CH_3COO^-	CH_3COOH	4.8
HS^-	H_2S	7.0
CN^-	HCN	9.2
HO^-	H_2O	15.7
H_2N^-	H_3N	35

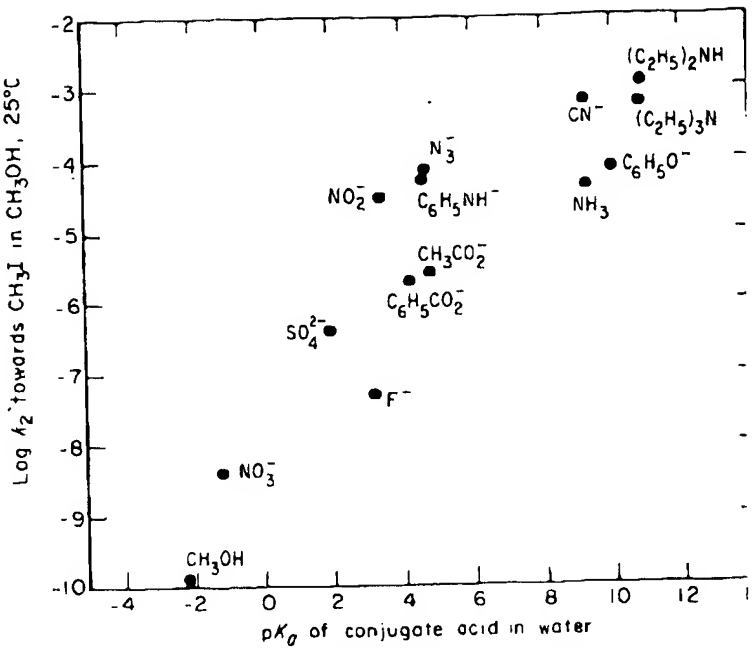


FIGURE 8.4 *Correlation of basicity with reactivity toward methyl iodide.*

There are a number of reasons why the correlation is not perfect. One is that we have compared reactions in two different solvents, a displac reaction in methyl alcohol and an acid-base equilibrium in water. Water a useful solvent for displacement reactions because most organic compour not sufficiently soluble. However, only a limited number of pK_a valu available for nonaqueous solvents.

Another reason why the correlation is not perfect is to be found in com the types of bonding in the two systems. In an acid-base equilibrium, th involved is to a small and relatively "tight" 1*s* orbital of a hydrogen (Figur In the transition state of a displacement reaction, the orbital containing th pair of the base overlaps instead with the larger, more diffuse, 2*p* orbit carbon (Figure 8.5b).

These two kinds of reactivity of a base are given different names. **Bas the affinity of a base for a proton,** and is measured by the equilibrium the conjugate acid in water. **Nucleophilicity** (from *nucleus,* L., kernel, and Gr., loving; hence, "nucleus-loving") **is the affinity of a base for a carbo**

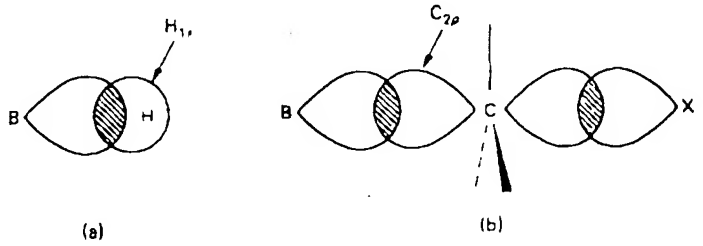


FIGURE 8.5 *Comparison of orbital overlaps of a base with a proton and w the central carbon of a displacement reaction*

in a displacement reaction transition state. Nucleophilicity is measured by the rate of reaction of the base with a suitable compound, usually methyl bromide or iodide, in some standard solvent.

The displacement reaction is often referred to as an S_N2 reaction for **substitution, nucleophilic, bimolecular.**

The **molecularity** of a reaction is defined as the number of molecules involved in the rate-determining transition state. It is sometimes, but not always, equal to the **kinetic order** of the reaction. For example, consider a reaction of the type

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow[\text{slow}]{k_2} D$$

The rate of appearance of the product D is given by the rate law

$$\text{rate of formation of D} = \frac{d[D]}{dt} = \frac{k_1 k_2}{k_{-1}}[A][B] = k'[A][B]$$

which shows second-order kinetics. However, in the slow step (k_2), the rate-determining step, only one molecule, species C, is involved. Hence, the reaction is unimolecular.

The mechanistic label S_N2 covers a wide variety of specific reactions (see, for example, Table 8.1 and Figure 8.4). All of the reactions in this category occur by the common mechanism discussed in this section. They all proceed with inversion of configuration at the reacting carbon, and they all show second-order kinetics. The rates of S_N2 reactions are markedly affected by a number of factors, including the nucleophilicity of the attacking group, the structural environment of the carbon where displacement occurs, the nature of the leaving group, and the nature of the solvent. The important principles that enter into evaluating the effect of these variables recur frequently in organic chemistry, and therefore warrant careful study at this time.

8.4 Nucleophilicity

In constructing Figure 8.4, only a fraction of the available data was used. In fact, the bases, or nucleophiles, used in that plot all involve reaction with atoms in the first row of the periodic table—C, N, O, F. The rough correlation evident in Figure 8.4 shows that *more basic electron pairs tend to be more nucleophilic.*

Now let us add more data and expand the plot to that shown in Figure 8.6. The points in Figure 8.4 have been retained as unlabeled open circles. The additional points for other nucleophilic reagents produce still more scatter. However, a second important generalization can be drawn from Figure 8.6. **Second- and third-row elements are invariably more nucleophilic than first-row elements of comparable basicity.** The reason for this generalization appears to be that the larger elements have relatively diffuse lone pairs that are more polarizable. These more diffuse lone pairs tend to bond more strongly to the more diffuse *p* orbital of the S_N2 transition state than to the small, tight 1*s* orbital of a hydrogen. Consequently, such lone pairs tend to be more nucleophilic than their basicity would indicate. The first-row elements have smaller orbitals and the lone pairs are held more tightly. These elements are relatively more basic and less nucleo-

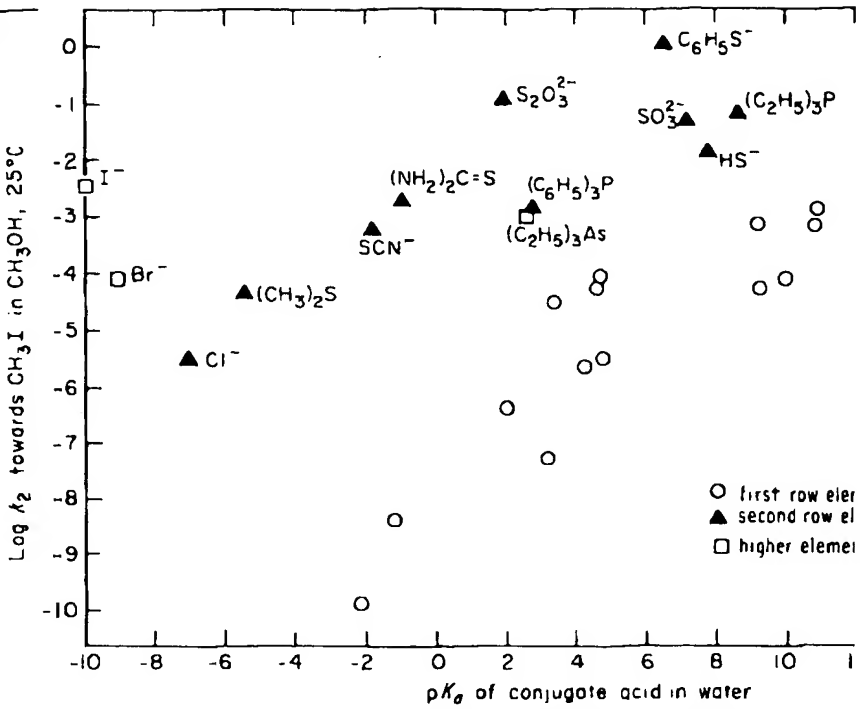


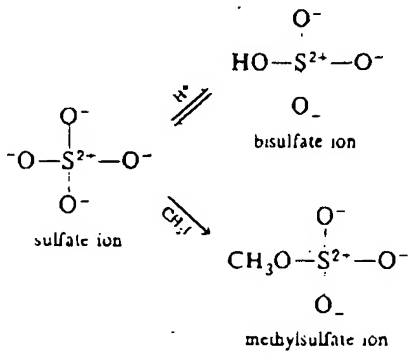
FIGURE 8.6 *Comparison of nucleophilicities and basicities of various reactants. Open circles refer to points in Figure* 8.4.

philic. Examples of reactivity towards methyl iodide are

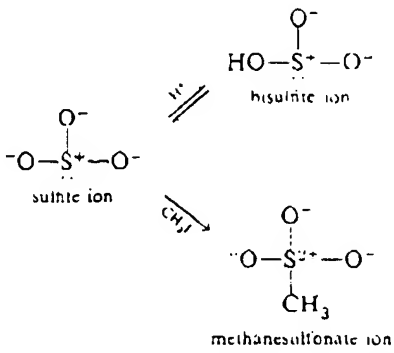
$$(CH_3)_2S > CH_3OH$$
$$HS^- > HO^-$$
$$Cl^- > F^-$$
$$C_6H_5S^- > C_6H_5O^-$$
$$(C_2H_5)_3P > (C_2H_5)_3N$$

In each case, the group with the first-row element is the more basic and l less nucleophilic.

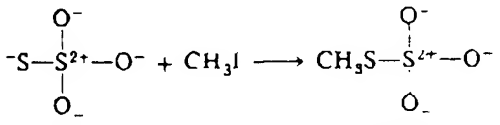
At this point we can now interpret an interesting experimental result. ion is straightforward in its reaction with either H^+ or CH_3I in an S_N2 re Both types of reaction occur at an oxygen



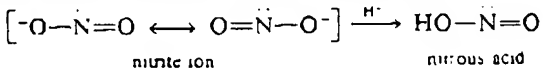
Sulfite ion, however, behaves quite differently. It reacts with a proton on oxygen to form bisulfite ion, and with methyl iodide on sulfur to form the methanesulfonate ion.



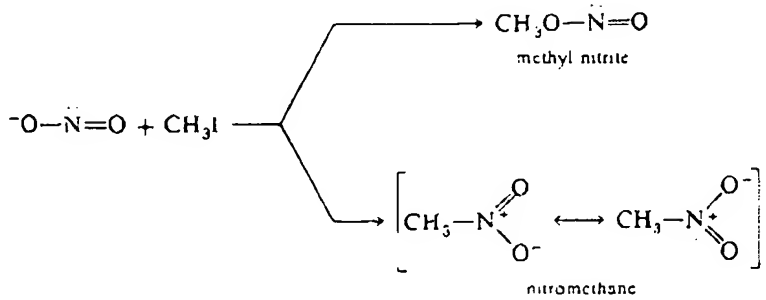
The oxygen in sulfite ion is the more basic atom and prefers to attack H^+, but the lone pair on sulfur is more nucleophilic, and it has preference in the S_N2 transition state. Sulfate ion has no lone pair on sulfur, and both reactions have no alternative but to occur at the oxygen. Thiosulfate ion is a simple sulfur analog of sulfate. This ion reacts with methyl iodide exclusively on sulfur, even though there are three oxygens and only one sulfur.



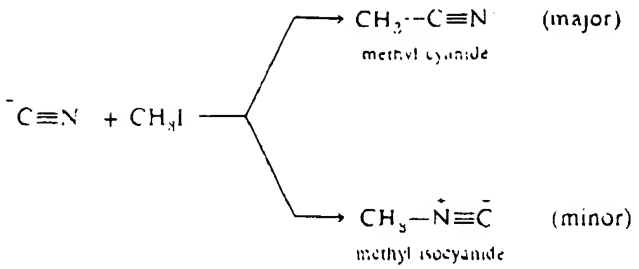
Finally, there are some nucleophiles that show measurable nucleophilic properties at two different atoms. Nitrite ion is an example. The ion undergoes protonation exclusively on oxygen to give nitrous acid.



However, the reaction of nitrite ion with methyl iodide gives both methyl nitrite and nitromethane.



In this case, both nitrogen and oxygen are first-row elements and have comparable nucleophilicities. The ratio of the products actually depends on the reaction conditions. Another example is the reaction with cyanide ion. In addition to methyl cyanide, the major product, small amounts of methyl isocyanide are also produced.



Anions such as these, which can react at two different positions, are **ambident** (*ambo*, L., both; *dentis*, L., tooth), "two-fanged" nucleophiles.

8.5
Effect of Substrate Structure on Displacement Reactions

A large variety of alkyl halides undergo substitution by the S_N2 mech The ease of reaction depends markedly upon the structure of the alkyl to which the halogen is attached. Reactivities vary widely and in a con manner Branching of the chain at the carbon where substitution occu α-carbon) has a significant effect on the rate of reaction Relative rates reactions for methyl, ethyl, isopropyl, and *t*-butyl halides are approxima shown in Table 8.3.

TABLE 8.3
Effect of Branching at the α-Carbon on the Rate of S_N2 Reactions

Alkyl Halide	Relative Rate
CH_3-	30
CH_3CH_2-	1
$(CH_3)_2CH-$	0.03
$(CH_3)_3C-$	≈ 0

These effects on reaction rate are interpreted with the concept of steric hin to attack of the attacking nucleophile. The rear of a methyl group is rel exposed to such attack. As the hydrogens of the methyl group are repla methyl groups, the area in the rear of the leaving group becomes more e bered. It becomes more difficult for the attacking group to approach enough to the rear of the C—X bond for reaction to occur, and the rate of re diminishes (Figure 8.7).

A similar effect may be seen in branching at the β-carbon. Some typical r rates are shown in Table 8.4. This reduction in rate is also attributable tc hindrance. In one conformation, the rear of a *n*-propyl carbon is seriously b (Figure 8.8a) but in two other conformations, the situation is no worse th ethyl (Figure 8.8b). Consequently, *n*-propyl halides undergo S_N2 displac only slightly less readily than do ethyl halides.

For the isobutyl group, it is possible to rotate both of the β-methyl grou of the way of the attacking group, but the resulting conformation is congested and has relatively high energy (Figure 8.9). Accordingly, is halides are much less reactive than either ethyl or *n*-propyl compounds.

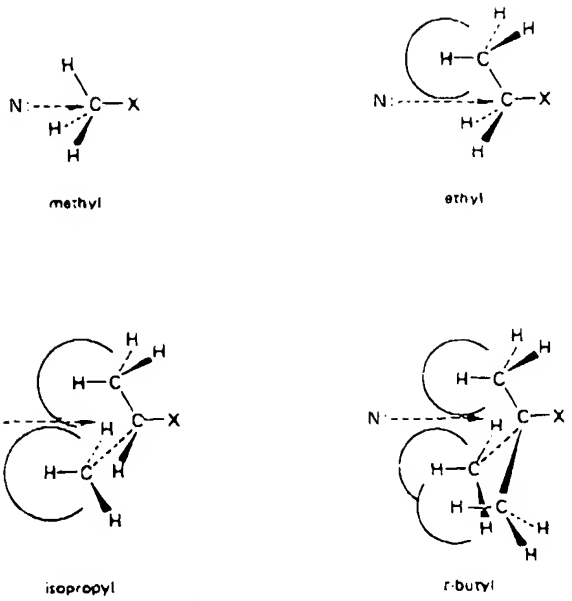


FIGURE 8.7 *Effect of α branching on S_N2 reactions.*

TABLE 8.4
Effect of Branching at the β-Carbon on the Rate of S_N2 Reactions

Alkyl Halide	Relative Rate
CH_3CH_2—	1
$CH_3CH_2CH_2$—	0.4
$(CH_3)_2CHCH_2$—	0.03
$(CH_3)_3CCH_2$—	0.00001

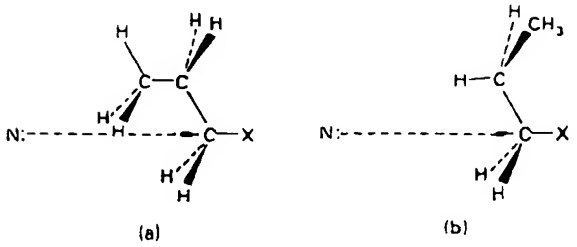


FIGURE 8.8 S_N2 *attack at two conformations of n-propyl compounds.*

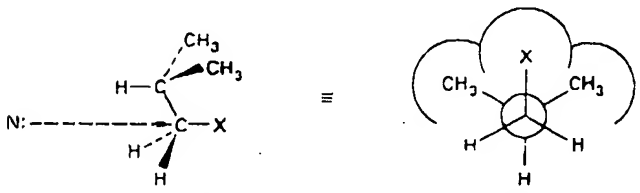


FIGURE 8.9 S_N2 *reaction at isobutyl systems*

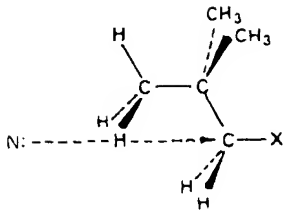


FIGURE 8.10 S_N2 *reaction at neopentyl compounds.*

Neopentyl halides are particularly interesting because there is no conform in which a blocking methyl group can be avoided (Figure 8.10). Neopentyl h are essentially unreactive in S_N2 reactions except under very drastic cond Substitution of sites more remote than the β-carbon have little or no eff the ease of S_N2 reactions. For example, *n*-butyl and *n*-pentyl halides re essentially the same rate as *n*-propyl halides.

The type of steric interaction we have discussed here forces groups to away from each other. Such deformation often forces orbitals to overla noncolinear fashion, which provides less effective bonding than colinear o (Figure 8.11). Overlap of orbitals that are not colinear gives bonds whicl be described as "bent." Such bent bonds are generally of higher energy th corresponding "straight bonds." These principles apply not only to the tra states for displacement reactions but to certain strained molecules as well (C 23).

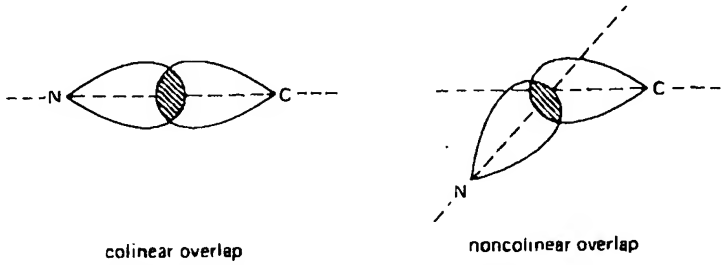


FIGURE 8.11 *Bent bonds have reduced orbital overlap.*

In summary, the effect of the structure of the alkyl group on the rate reaction is apparent in two ways.

1. **Branching at the α-carbon hinders reaction: rate order is methyl mary > secondary $\gg$ tertiary.**
2. **Branching at the β-carbon hinders reaction: neopentyl compounds are ularly slow.**

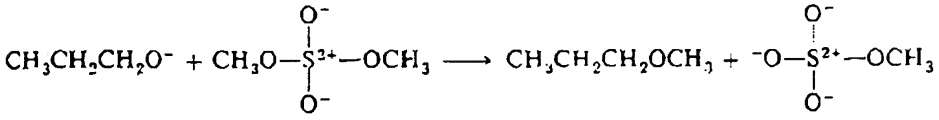
Displacements that proceed by the S_N2 mechanism are most successfu primary compounds having no branches at the β-carbon. Yields are poor with secondary halides and with primary halides having branches at C-2 pentyl systems undergo the reaction only under very drastic conditions and t halides do not react by this mechanism at all. When the rate of the S_N2 re is slowed down by these structural effects, alternative side reactions be compete. With tertiary halides, and to an important degree with seconda highly branched primary halides, the side reactions tend to dominate. The reactions are discussed in Sections 8.7 and 8.8.

8.6 Some Typical S_N2 Reactions

A. *Leaving Groups*

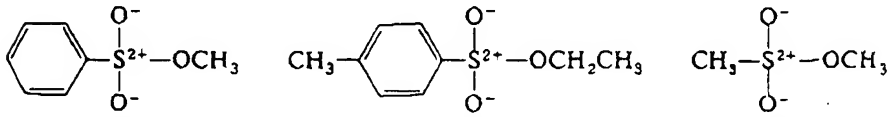
Alkyl chlorides, bromides, and iodides all react satisfactorily by the S_N2 mechanism. The ease of reaction is dependent on the nature of the **leaving group**, alkyl iodides reacting most rapidly and alkyl chlorides most slowly. Alkyl fluorides are essentially unreactive by the S_N2 mechanism. Since chlorine is much cheaper than bromine, alkyl chlorides are the least expensive alkyl halides. However, for laboratory uses where only small amounts of material are involved, alkyl bromides are commonly used because they are 50–100 times more reactive than the corresponding chlorides. Iodides are somewhat more reactive than bromides but are quite a bit more expensive, and this slightly increased reactivity does not justify their additional cost. In industrial processes, where massive amounts of materials are involved and cost is a prime consideration, alkyl chlorides are used almost exclusively.

The S_N2 reaction is not restricted to alkyl halides. Any group that is the conjugate base of a strong acid can act as a leaving group. An example is bisulfate ion, HSO_4^-, which is the conjugate base of sulfuric acid, pK_a − 5. Dimethyl sulfate is an inexpensive commercial compound that reacts readily by the S_N2 mechanism. The leaving group is the methylsulfate ion, which is similar in its base strength to bisulfate ion.



methylsulfate ion

The chief disadvantage of dimethyl sulfate is its toxicity. It is water soluble and reacts readily with the nucleophilic groups in body tissues and fluids. Although dimethyl sulfate is the only sulfate in common use, alkyl sulfonates are often employed. Sulfonic acids, RSO_2OH, are similar to sulfuric acid in acidity and the sulfonate ion, RSO_3^-, is an excellent leaving group. Alkyl benzenesulfonates, alkyl *p*-toluenesulfonates, and alkyl methanesulfonates are extremely useful substrates for S_N2 reactions. These compounds are readily prepared from alcohols as described in Sections 11.7.D and 18.13.A.



methyl benzenesulfonate

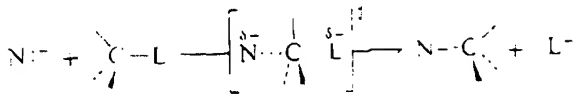
ethyl *p*-toluenesulfonate

methyl methanesulfonate

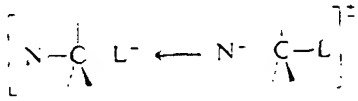
Alkyl nitrates undergo reaction by the S_N2 mechanism because nitric acid is a strong acid and nitrate ion is a weak base. However, alkyl nitrates are more prone to side reactions than the corresponding halides and, therefore, the yield of substitution product is lower. Consequently, nitrates are rarely used.

The facility with which a group can function as a leaving group in an S_N2 reaction is related to its **basicity**. If a group is a weak base (that is, the conjugate base of a strong acid), it will generally be a "good" leaving group. This is readily

understood by considering the electronic structure of the transition state.



The negative charge which is introduced with the attacking nucleophile is d uted over several atoms in the transition state. The charge is borne mos the entering and leaving groups, as shown by the resonance structures f transition state



The leaving group has gained an appreciable amount of electron den going from reactant to transition state. The more this electron density or ne charge is stabilized, the lower is the energy of the transition state and the is the rate of reaction. The degree to which a group can accommodate a ne charge is also related to its affinity for a proton, its basicity. The acids HC HI, and H_2SO_4 are all strong acids because the anions Cl^-, Br^-, I^-, and are stable anions. These anions are also good leaving groups in S_N2 rea

HCN is a weak acid ($pK_a = 10$) and the displacement of cyanide is observed.

$$N:^- + RCN \not\longrightarrow R{-}N + CN^-$$

Hydrazoic acid (HN_3) and acetic acid (CH_3CO_2H) are also weak acids (] 5.8 and 4.8, respectively). Correspondingly, azide ion and acetate ion are ext poor leaving groups.

$$N:^- + R{-}N_3 \not\longrightarrow RN + N_3^-$$

$$N^- + R{-}O\overset{\overset{O}{\|}}{C}CH_3 \not\longrightarrow RN + CH_3CO_2^-$$

The reason that alkyl fluorides are ineffective substrates in the S_N2 rea related to the relatively low acidity of HF ($pK_a = 3$)

By comparing S_N2 reactivity with relative acidity, we can understa operation of **acid catalysis** in certain displacement processes. Alcohols undergo S_N2 reactions because hydroxide ion is too basic (the pK_a of its co acid, H_2O, is 15.7).

$$N^- + R{-}OH \not\longrightarrow R{-}N + OH^-$$

However, in the presence of a strong mineral acid, such as HCl, HBr, or the alcohol oxygen is protonated. An S_N2 reaction can now occur beca leaving group is water, which is a much weaker base than OH^- (the cc acid of water, H_3O^+, has $pK_a = -1.7$).

$$R{-}OH + H^+ \rightleftharpoons R{-}\overset{+}{O}H_2 + N:^- \longrightarrow R{-}N + H_2O$$

Note that the same principles of electron density and relative basicity are i in this reaction, even though the leaving group is not an anion. This is and important reaction of alcohols and it will be developed more fully in 11.7.

B. *Solvents*

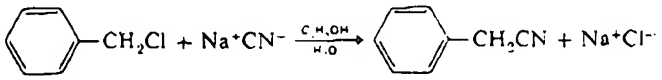
A number of solvents may be used as reaction media for S_N2 reactions. Ethanol and methanol are particularly useful because they are inexpensive, relatively inert, and dissolve many organic substrates and inorganic salts. Sometimes some additional water is added to increase the solubility of the inorganic salt used as the displacing agent. Some typical examples follow

$$CH_3O^- + CH_3CH_2CH_2CH_2Br \xrightarrow{CH_3OH} CH_3CH_2CH_2CH_2OCH_3 + Br^-$$

n-Butyl bromide is refluxed with sodium methoxide in methanol for ½ hr. Water is added and the organic layer is separated, dried, and distilled to give methyl *n*-butyl ether.

$$Na^+SCN^- + CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[H_2O]{C_2H_5OH} CH_3\underset{\displaystyle SCN}{\underset{|}{C}}HCH_3 + Na^+Br^-$$

Isopropyl bromide and sodium thiocyanate (NaSCN) are refluxed in 90% aqueous alcohol for 6 hr. The precipitated sodium bromide is filtered. The filtrate is diluted with water and extracted with ether. Distillation gives isopropyl thiocyanate, $(CH_3)_2CHSCN$, in 76–79% yield



Benzyl chloride, $C_6H_5CH_2Cl$, is refluxed with sodium cyanide for 4 hr in aqueous alcohol. The sodium chloride is filtered, the solvent is distilled and the product benzyl cyanide, $C_6H_5CH_2CN$, is distilled under vacuum to give a 80–90% yield. Sodium and potassium cyanides are highly toxic white solids that are very soluble in water and slightly soluble in ethanol. Organic cyanides may be hydrolyzed to carboxylic acids (Section 17.6).

The use of acetone as a solvent for halide exchange reactions was illustrated at the beginning of this chapter. Acetone is an example of a **polar aprotic** solvent, that is, a solvent without hydroxy groups but with a relatively high dipole moment and dielectric constant. Polar aprotic solvents are useful because of their ability to solvate ions and, thereby, to dissolve many salts. Other examples are acetonitrile, CH_3CN; dimethylformamide, $(CH_3)_2NCHO$; dimethyl sulfoxide, $(CH_3)_2SO$; and hexamethylphosphoric triamide, $[(CH_3)_2N]_3PO$.

Displacement reactions in polar aprotic solvents are frequently much faster than they are in hydroxylic solvents. For example, the reaction of methyl bromide with iodide ion is about 500 times faster in acetone than in methyl alcohol. An even more striking example is the reaction of chloride ion with methyl iodide, which is a *million times* faster in dimethylformamide than it is in methyl alcohol. The relative rate of reaction of azide ion with *n*-butyl bromide in various solvents is shown for comparison in Table 8.5. One important reason for this effect is hydrogen bonding. In a hydroxylic solvent, the OH groups can solvate anions by hydrogen bonding:

$$ROH\text{---}X^-\text{---}HOR$$

Hydrogen bonding will be discussed in detail in Section 11.3. For the present, suffice it to say that such bonding tends to tie up an anion and make it less reactive. Aprotic solvents have no hydrogens capable of hydrogen bonding. Hence, the anions are more free and have greater effective nucleophilicity.

TABLE 8.5
Relative Rates for the Reaction
$N_3^- + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9N_3 + Br^-$

Solvent	Relative Rate
CH_3OH	1
$(CH_3)_2SO$ (DMSO)	1,300
$(CH_3)_2NCHO$ (DMF)	2,800
CH_3CN	5,000
$[(CH_3)_2N]_3PO$ (HMPT)	200,000

This type of solvation effect can even change the relative reactivities of nucleophilic groups. For example, the order of reactivity of halide ior reaction in water or in alcohols is

$$I^- > Br^- > Cl^-$$

In acetone, the reactivities tend to be closer together and in dimethylfc the order is even reversed! More basic anions tend to be hydrogen bon firmly and are less reactive in hydroxylic solvents. Consequently, nucle is not a simple and invariant property, but depends on the specific conditions, and solvents. We make frequent use of qualitative rather tha tative generalizations, and it is still useful to know that iodide ion is more reactive than chloride ion, and that second-row elements are usu reactive in displacement reaction than first-row elements. Even thou are generally more reactive in polar aprotic solvents than in aqueou the aqueous solvents are still frequently used in practice because th expensive, convenient, and, for many reactions, serve perfectly adeq

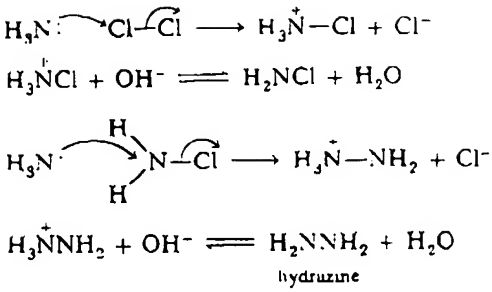
C. *Displacement Reactions at Atoms Other than Carbon*

Displacement reactions are very common and may occur at atoms carbon. Many well-known inorganic reactions can be formulated as n displacement reactions. One example is the formation of hypochlorite bleach) by the reaction of hydroxide ion with chlorine. The reacti considered as an S_N2 reaction in which hydroxide ion displaces chlorid a chlorine molecule

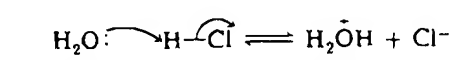
$$HO:^- \rightarrow Cl\text{—}\overset{\curvearrowright}{Cl} \longrightarrow HOCl + Cl^-$$

The preceding equation illustrates the use of arrows for "electron-pushi device for keeping track of electron pairs when describing the bond rec that occur during a reaction. An arrow symbolizes the flow of an elec a reaction. The arrow begins at the electron pair in a reactant and poi the electron pair "goes" in the reaction. In the example given, an elec hydroxide ion attacks a chlorine and forms a new covalent bond. At th the electron pair that had bonded the two chlorines together is released with the leaving chloride ion. It is conventional to use curved arrows.

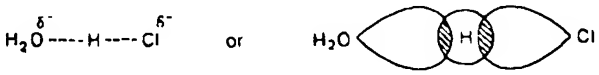
Another example is the Raschig process for the synthesis of hydra involves two such displacement steps.



Even ordinary acid-base reactions can be regarded as displacement reactions on hydrogen.

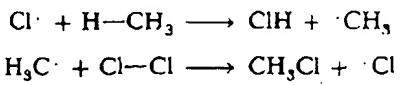


Such reactions are extremely rapid and we generally consider them only as facile equilibria. However, with special techniques, the rates of proton transfer reactions can be measured, even though the second-order rate constants are as high as $10^{10}\,M^{-1}\,\text{sec}^{-1}$. This is many orders of magnitude faster than the analogous second-order rate constants for displacements on carbon. The transition state for such a proton-transfer reaction may be formulated as



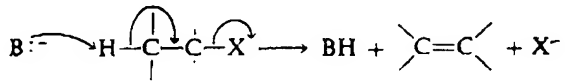
In such a transition state the 1*s* orbital of the hydrogen is partially bound to both the incoming and the leaving base.

Many reactions of atoms and radicals with molecules can be regarded as radical displacement reactions. Mechanistically, such displacements are classified as **bimolecular homolytic substitution** reactions, S_H2. We have already discussed such reactions in Chapter 5, but now they take their place in a family of related reactions.



8.7 E2 Elimination

One of the side reactions that occurs in varying degree in displacement reactions is the elimination of the elements of HX to product an alkene.



Under appropriate conditions, this reaction can be the principal reaction and becomes a method for preparing alkenes. Accordingly, it is discussed in more detail in Section 12.5.A. For the present, it suffices to know that this reaction occurs by attack of a base on a hydrogen with concommitant formation of a C=C double bond and breaking of the C—X bond to form halide ion.

Mechanistically, the reaction is classified as **bimolecular elimination**, or **E2**. Since

4. Transesterification (Section 18.9.B).

$$RCOR' + R''OH \xrightarrow[R''O^-]{H^+ \text{ or}} RCOR'' + R'OH$$

5. Acyl halides and alcohols (Section 18.9 B).

$$RCCl + R'OH \longrightarrow RCOR' + HCl$$

6. Acid anhydrides and alcohols (Section 18.9.B)

$$RCOCR + R'OH \longrightarrow RCOR' + RCOH$$

Amides

1. Pyrolysis of ammonium carboxylates (Section 17.7.C)

$$RCO^-NH_4^+ \xrightarrow{\text{heat}} RCNH_2 + H_2O$$

$$RCO^-R'NH_3^+ \xrightarrow{\text{heat}} RCNHR' + H_2O$$

2. Acyl halides and ammonia or amines (Section 18.9.C)

$$RCCl + 2\,NH_3 \longrightarrow RCNH_2 + NH_4^+\,Cl^-$$

3. Acid anhydrides and ammonia or amines (Section 18.9.C)

$$RCOCR + R'NH_2 \longrightarrow RCNHR' + RCO_2H$$

4. Partial hydrolysis of nitriles (Section 18.9.A)

$$RC{\equiv}N + H_2O \xrightarrow[\text{or } OH^-]{H^+} RCNH_2$$

Acyl Halides

1. Carboxylic acids with $SOCl_2$ (Section 17.7.C).

$$RCOH + SOCl_2 \longrightarrow RCCl + SO_2 + HCl$$

2. Carboxylic acids with PCl_5 (Section 17.7.C).

$$RCOH + PCl_5 \longrightarrow RCCl + POCl_3 + HCl$$

3. Carboxylic acids with PBr_3 (Section 17.7.C)

$$3\,RCOH + PBr_3 \longrightarrow 3\,RCBr + H_3PO_3$$

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